REMARKS

In the Office Action, the Examiner provides a final rejection of claims 45-67, 69, 77-87, and 89 under 35 U.S.C. 103(a). Claims 45-67, 69, 81-87, and 89 are pending in this application. Claims 1-44, 68, 70-76, and 88 are cancelled. Claims 77-80 are withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group.

Request for Withdrawal of Finality of Rejection

Applicants request reconsideration and withdrawal of the finality of the rejection of the Office Action because Applicants' amendment did not necessitate the current rejection. According to the M.P.E.P., "second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement ... ." M.P.E.P. § 706.07(a). In this case, the Applicants' amendment of the claims in the Amendment dated June 13, 2006, did not necessitate the current rejection. Applicants amended claims 45, 46, 50, 55, 56, and 60 to include "wherein the presence, concentration, or activity of said enzyme or said factor is not known;" claim 51 to specify a covalent bond "between said first substrate and said second substrate;" claim 81 to change "comprises" to "consists essentially of;" and claim 86 to change "electrode" to "metal." Amendment dated June 13, 2006, at pages 2-10.

Applicants amendment of claims 45, 46, 50, 55, 56, and 60 to include "wherein the presence, concentration, or activity of said enzyme or said factor is not known" did not necessitate the current rejection. This amendment narrows claims 45, 46, 50, 55,

56, and 60 by adding this limitation. The new rejections could equally have been made on the claims before this amendment, therefore this amendment did not necessitate the current rejection. The finality of the rejection should be removed.

In addition, none of the amendments by Applicants necessitated rejection over Shukla et al. in view of Massey et al. Shukla et al., 22(9) Nucleic Acids Res. 1626-31 ("Shukla"); Massey et al., U.S. Patent No. 5,866,434 ("Massey"). The new rejection does not focus on the amendment to the claims, but on the claims generally. In fact the new rejection parallels a previous rejection: namely, the rejection over Shivaraja and Massey. See Office Action dated February 23, 2006. The new rejection substitutes Shukla for Shivaraja in the previous rejection.

The current rejection parallels the previous rejection in that Shukla describes an activity gel assay for the detection of DNA helicases in crude extracts. *See* Shukla at page 1626. Similarly, Sivaraja teaches using conventional assays to measure the activity of a helicase. Shukla further notes that purified protein samples of DNA helicases, endonucleases, and exonucleases also produced activity. Massey is common to both rejections. Massey describes a binding assay where the analyte of interest remains bound to the assay-performance substance. *See* Massey, col. 13, lines 9-57. Massey's assay simply measures binding, not enzymatic activity.

Applicants respectfully request reconsideration and withdrawal of the finality of the rejection because the amendment of the claims in the Amendment dated June 13, 2006, did not necessitate the current rejection. Applicants amendment the claims in the Response dated June 23, 2006, and overcame the rejection over Sivaraja in view of Massey. Office Action page 2 (noting that "[a]ll arguments and amendment have been

fully considered and thoroughly reviewed and deemed persuasive in view of the amendment").

The Claims Are Not Obvious Over Shukla and Massey

The Examiner rejects claims 45-67, 69, 81-87, and 89 under 35 U.S.C. 103(a) over Shukla in view of Massey.

According to the Examiner, "[i]t would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of assaying enzyme activity as taught by Shukla et al. with a step of luminescent label on an electrode as taught by Massey et al. for the purpose of enhancing the efficiency of detecting the enzyme activity in said sample." Office Action, page 6.

According to the M.P.E.P.,

> [t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P. § 2142.

The References Do Not Teach All Claim Limitations

Applicants respectfully disagree with the characterization of Shukla and Massey by the Examiner. In particular, with respect to claims 45-54, 69, 81-82, 85-87, and 89 as directed to the joining of two substrates, Shukla does not describe an assay for a joining activity. Shukla describes a gel assay for the detection of DNA helicases and nucleases from cell-free extracts. It relies on the ability of DNA helicases to unwind

radioactive fragments from single-stranded M13 circles that were immobilized in an SDS polyacrylamide gel. Shukla, page 1626. The radioactive fragments, freed from the M13 circles, are then electroblotted to a nylon membrane. The assay does not involve the joining of a first and second substrate as in claims 45-54, 81-82, and 89 or as described in the joining portion of claims 69 or 85-87. In fact the, assay involves separation of two noncovalently bonded strands from a single substrate – the radiolabeled partially duplex M13mp18 DNA.

Moreover, Applicants respectfully disagree with the Examiner's characterization of Massey. The Examiner states that Massey "teach[es] a method of claims 45-46, 50, of assaying a sample for an activity that modifies the rate of joining that joins (binds) a first substrate (an assay-performance substance) and a second substance (a functionalized graphic nanotube) to form a product (binding complex) ...." Office Action, page 4. Massey describes the direct binding of an analyte of interest to a "functionalized, graphitic nanotube." It does not describe nor suggest the use of this assay to measure an enzymatic activity for joining two substrates together. Applicants believe that the Examiner is equating binding to the enzymatic joining reaction described in the instant application. In a binding assay, there is no third substance performing or catalyzing the joining activity, which is absolutely required in an assay designed to measure an enzyme activity that joins two substrates. Further, an enzyme is catalytic in nature, and thus, does not form part of a complex, unlike the nanotube or assay-performance substance of Massey as cited at col. 13. Element (b) in claims 45, 46, and 50 make this difference explicit by requiring that "said enzyme or factor is not part of the product." Since, claims 45-46 and 50 of the instant application require that

the invention assay for an enzyme that joins two substrates, there is no reason why one skilled in the art would be motivated to combine Shukla with Massey.

In addition, Applicants respectfully disagree with the assertion of the Examiner on page 5 of the Office Action that "[w]ith regard to claim 46-47, 85, Massey et al. teach that said first substrate is linked to a luminescent label (see col 13, line 15-17) and said second substrate linked (attached) to electrode (magnetically responsive nanotubes) (see col. 13, line 18-19)," because claim 85 requires the electrode to consist "essentially of a metal" and thus cannot be a carbon nanotube. Further, Applicants respectfully disagree with the assertion of the Examiner on page 6 of the Office Action that "[w]ith regard to claim 65-66, 89, Massey et al. teach that said electrode comprises elemental carbon in the form of graphite (see col. 13, line 18-19)," because claim 89 requires the electrod be not a carbon electrode.

Finally, claims 55-64, 83-86, and 89 require the electrode not to be a carbon electrode, but this claim limitation is not present in Massey or Shukla. According to the Examiner, "Massey et al. teach that said electrode comprises elemental carbon in the form of graphite (see col. 13, line 18-19)." Office Action at 6. Also according to the Examiner, Shukla et al. also does not teach the electrode not to be a carbon electrode: "However, Shukla et al. did not teach measuring said enzyme activity using a luminescent label immobilized on an electrode ... ." Office Action at 4. In fact, Shukla does not disclose any electrodes. Niether reference accounts for the non-carbon electrode limitation of these claims.

Thus, neither alone nor in combination do Shukla and/or Massey teach all of the limitations of claims 45-54, 69, 81-82, 85-87, and 89. Both references fail to teach an assay for a joining activity.

Shukla and Massey Provide No Suggestion or Motivation To Modify or Combine

In addition, with respect to claims 45-67, 69, 81-87, and 89, Shukla provides no motivation to combine its teachings with Massey because no problem was perceived. The Federal Circuit case, *Winner v. Wang*, states that in order to find a motivation to modify a reference, there must be some deficiency or problem perceived with the prior art reference. 53 U.S.P.Q.2d 1580, 1587 (Fed. Cir. 2000) (stating "there was no apparent disadvantage to the dead-bolt mechanism of Johnson, and therefore the motivation to combine would not stem from the "nature of the problem" facing one of ordinary skill in the art, because no "problem" was perceived).

The Examiner alleges that a person of ordinary skill in the art at the time the invention was made would have been motivated to modify the gel assay of Shukla with the electroluminescent binding assay of Massey for the purpose of enhancing the efficiency of detecting the enzyme activity and increasing the sensitivity of detection. Office Action, page 6.

With respect to efficiency, Shukla notes that "the apparent disadvantage in the time-course of the gel assay is more than compensated for by its direct applicability to unfractionated extracts." Shukla, page 1631. Further, the same "apparent disadvantage" of Shukla requiring fractionation with a gel would be present in Massey.

In fact, Massey provides no fractionation analogous to the gel Shukla permitting application to unfractionated extracts.

With respect to sensitivity, Shukla notes that "the inability to detect particular DNA helicases was expected based on the characteristics of these enzymes in the standard helicase assay." *Id.* Shukla notes that "these limitations in the sensitivity of the activity gel assay can be overcome easily by substituting the appropriate substrates." *Id.* In particular, Shukla notes that "[t]he DnaB and the PriA DNA helicases could not be detected in the activity gel assay in part because they required a particular structure or sequence that was not in the activity gel DNA substrate." Similarly, Shukla notes that of DNA helicase III was not detected because it migrated to a region of the gel that was heavily populated with nuclease activities. Shukla suggests that a 2-dimensional activity gel could eliminate this problem. Massey provides no method to eliminate this problem.

Contrary to the Examiner's allegation, there is no motivation to combine the gel assay for the detection of DNA helicases and nucleases from cell-free extracts of Shukla with the electrochemiluminescent binding assay of Massey.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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